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Filed : **March 12, 2001**

REMARKS

The Applicants have amended Claims 1, 21, and 24. The specific changes to the amended claims are shown above, wherein the insertions are underlined and the ~~deletions are stricken through~~. The Applicants respond below to rejections and objections raised by the Examiner in the Office Action of October 21, 2002.

I. Objections to Informalities

The Examiner has objected to the Specification because three co-pending U.S. patent applications which are incorporated by reference at page 1 lines 10-21 are not identified by application numbers. The Applicants submit that the present amendment to the Specification includes the three U.S. Patent application numbers. The Applicants respectfully submit that the amendment to the Specification does not add any new matter.

II. Rejections under 35 U.S.C. § 112

The Examiner has rejected Claims 24-25 under 35 U.S.C. § 112, second paragraph, as being indefinite with regard to the term "insignificant." The Applicants respectfully submit that in its amended form, Claim 24 no longer recites the term "insignificant."

Next, the Examiner has asserted that Claim 1 is vague and indefinite with regard to the term "biological activity." The Examiner notes that various biological activities can be attributed to a compound and indicates that such activity could include "transportation throughout a cell, effects on osmotic pressure, or non-specific binding." The Applicants agree that a compound can exhibit several "biological activities," including those the Examiner has recited. The Applicants disagree, however, that Claim 1 is vague or indefinite. The Applicants note that breadth of a claim should not be equated with indefiniteness. *See In re Miller*, 441 F.2d 689 (CCPA 1971). The Applicants respectfully submit that, based on the language of Claim 1, those of skill in the art will appreciate that a variety of biological activities, whether presently known or unknown, can be characterized for a candidate compound in accordance with the present invention.

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III. Rejections under 35 U.S.C. § 103

Claims 1-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gonzalez *et al.* 1995 in view of Renier *et al.* 1995. The Applicants respectfully traverse.

Gonzalez *et al.*

Gonzalez *et al.* describe a technique for depolarizing a membrane potential and using a fluorescent dye to monitor movement across the membrane and cellular transmembrane potential. To effect the electrical potential change in the cell, the reference teaches the use of patch clamping, a technique in which a cell is contacted and then immobilized or "clamped" with a patch pipette. Once the cell is immobilized, a voltage can be applied that will alter the membrane potential of the cell.

Renier *et al.*

Renier *et al.* disclose a technique for evaluating the expression of CFTR, a protein associated with cystic fibrosis. The technique relies on fluorescent detection to determine whether a probe moiety has crossed a membrane as an indication of the presence or absence of activated CFTR protein.

The Prior Art of Record Fails to Teach or Suggest the Claimed Invention:

The prior art of record does not teach or suggest all of the elements of Claim 1 or Claim 21. As the dependent claims are all based on these two independent claims, they are patentable for at least the same reasons.

With regard to Claim 1, neither Gonzalez *et al.* nor Renier *et al.* disclose or suggest activity assays that involve: exposing one or more cells to a compound, exposing the cells to electric fields without the use of a patch clamp to effect a controlled change in membrane potential, and monitoring the transmembrane potential without the use of a patch clamp to characterize the biological or biochemical activity of the compound.

Gonzalez *et al.* only exposes cells to electric fields to test the performance of the voltage sensitive fluorescent dyes, and does so only with a patch clamp. The Applicants note that the Examiner has cited Gonzalez *et al.* as teaching applying a step potential to neonatal cardiac myocytes to activate voltage gated ion channels. The Applicants respectfully submit, however, that such an interpretation mischaracterizes Gonzalez *et al.* since the myocytes described in the reference were beating spontaneously. *See* Gonzalez *et al.* at 1277-78. Accordingly, Gonzalez *et*

al. does not teach using electrical methods to stimulate myocytes. In any case, the cells were not exposed to any compound, so there can be no teaching that the activity of such a compound was evaluated.

The teachings of Renier *et al.* suffer from similar deficiencies. No electric field is applied at any time, either with or without a patch clamp. Instead, Renier *et al.* teach that the membrane potential and the movement of a probe across the membrane is based on the presence of CFTR and the activity of protein kinase A. Thus, Renier does not cure the deficiency of Gonzales *et al.*

Accordingly, neither Gonzalez nor Renier, either alone or in combination, teach or suggest exposing one or more cells to a compound, exposing the cells to electric fields without the use of a patch clamp to effect a controlled change in membrane potential, and monitoring the transmembrane potential without the use of a patch clamp to characterize the biological or biochemical activity of the compound.

Next, the prior art of record does not teach or suggest all of the elements of Claim 21. In particular, there is no teaching or suggestion of: expressing a target ion channel in a population of cells, exposing the population of cells to a compound, exposing the population of cells to an electric field to effect a controlled change in transmembrane potential, and monitoring changes in the transmembrane potential of the population of cells to characterize the biochemical activity of the compound.

In the prior art of record, when conducting an experiment in which a potential is applied to a cell, only one cell at a time can be evaluated. This is due in part to the prior art use of patch clamping, a methodology described above in which a single cell is contacted and held in place with a pipet. The Applicants respectfully submit that exposing a population of cells to an electric field is not an obvious variation of exposing one cell to an electric field, particularly where the electric field is able to effect a controlled change in the transmembrane potential of cells.

As indicated above, patch clamping is a technique in which one cell at a time is clamped, stimulated, and measured. By teaching a technique that relies on patch clamping, Gonzalez *et al.* teach mechanical contact and modification of individual cells. They do not teach or suggest exposing an electric field to more than one cell at a time. As Renier *et al.* does not teach the application of any electric field, it does not cure the deficiencies of Gonzales *et al.* with respect to Claim 21 either.

Prior to the present invention, no technique had been found to successfully effect a controlled change in transmembrane potential to a population of cells such that the technique would be suitable for high throughput screening of drug candidate compounds. To the extent patch clamping techniques can be used to control transmembrane potential, these techniques are far to slow and costly to be used for high throughput screening. To the extent other ways to apply electric fields have been used in other contexts, none have ever been utilized for accurate membrane potential control so as to be used in a high throughput assay.

In some embodiments of the present invention, the electric field is a substantially uniform external (non contact) electric field across the cell or population of cells. This stands in contrast to patch clamping, wherein a voltage is applied across the membrane of a single cell and the response currents are measured.

Further, non-patch clamp methods to effectively stimulate cells containing ion channels to give a controllable membrane potential change can be used advantageously in conjunction with high-throughput analysis. Suitable ion channel assays for this purpose were previously unavailable.

None of the cited references, either alone or in combination, disclose, teach, or suggest the presently claimed invention. Since a number of the elements of the independent claims are not disclosed or suggested by the cited references, the references either alone or in combination do not render obvious the claimed invention. Therefore, the Applicants respectfully request the Examiner to reconsider and withdraw the rejections. Claims 1-29 are pending in the application. The Applicants respectfully submit that all claims are now in condition for allowance.

CONCLUSION

The Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims pursuant to the Examiner's rejections under §§ 112 and 103, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of these amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested.

Any claim amendments which are not specifically discussed in the above remarks are not made for patentability purposes, and it is respectfully submitted that the claims satisfy the

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statutory requirements for patentability without the entry of such amendments. These amendments have only been made to increase claim readability, to improve grammar, or to reduce the time and effort required of those in the art to clearly understand the scope of the claim language.

If the Examiner has any questions which may be answered by telephone, he is invited to call the undersigned directly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: 4-15-03

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